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Pigazzani, Filippo; Mackenzie, Isla; MacDonald, Thomas M.

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COMMENTARY

Ibuprofen and Paracetamol: Acceptably Safe for All?

Filippo Pigazzani[1] · **Isla Mackenzie**[1] · **Thomas M. MacDonald**[1]

In recent years, further concerns have been raised about the cardiovascular (CV) safety of non-steroidal anti-inflammatory drugs (NSAIDs) since the first signal was raised about rofecoxib [1]. A wide range of observational studies have demonstrated the increased risk of cardiac events in NSAIDs users. However, in both the prescription and non-prescription setting, NSAIDs remain among the most commonly used drugs and the uncertainty around their CV safety has prompted calls for new and more reliable evidence.

In the current issue of *Drug Safety*, Duong et al. [2] report hospital admissions for acute coronary syndrome (ACS), in a French claims database sample, that occurred within 3 months after the dispensing of ibuprofen or paracetamol. A cohort of 168,400 people prescribed 315,269 ibuprofen treatment episodes (TEs) were compared, using propensity score matching, with a cohort of 395,952 patients with 630,457 prescriptions for paracetamol TEs. Across the 3-month follow-up period, the rate of CV events was similar in each cohort. However, in the first 15 days of treatment there were 2.4/10,000 events in ibuprofen users versus 1.3/10,000 in paracetamol users, giving a hazard ratio of 1.7 [95% confidence interval (CI) 1.1–2.6]. This difference was driven by the subgroup of low-dose aspirin users (5% of the total study population), probably because aspirin is prescribed to high CV risk patients or patients with established CV disease. This is either due to direct toxicity from ibuprofen or to an interaction between ibuprofen and aspirin that results in reduced antiplatelet activity of aspirin in high-risk subjects [3]. However, in the following 15 days, the rate of events switched to being higher in paracetamol users, possibly because of a depletion of susceptible patients in the first 2 weeks of ibuprofen use. Of course, such subgroup analysis results could simply be due to random variation, but these results do suggest that ibuprofen would be best avoided in users of low-dose aspirin. This overall finding that ibuprofen and paracetamol are similar with regards to CV safety is, however, somewhat reassuring for ibuprofen users.

These observational studies are likely to have good external validity as subjects are likely to be representative of usual healthcare practice. However, observational data suffer from channeling and other biases [4] such that high-risk patients are given the perceived safer CV drug (paracetamol) whereas low-risk patients are given the perceived riskier NSAID (ibuprofen). Indeed, age is a dominant CV risk factor and the subjects in the study by Doung et al. [2] taking paracetamol were 10 years older than ibuprofen users.

Recently, two large randomized studies considering CV risk with NSAIDs have been reported. These studies have better internal validity but are less externally valid as subjects who participate in trials are more likely to be interested in their health and thus have lower CV risk overall.

The first study, the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen) trial, was a large randomized controlled trial ($n = 24{,}081$) of CV safety of celecoxib versus ibuprofen or naproxen in patients with arthritis and at moderate CV risk. PRECISION formally showed that the selective NSAID (celecoxib) had similar CV risks (was non-inferior) to the non-selective NSAIDs (ibuprofen and naproxen). However, subgroup analysis of the adjudicated outcomes showed that the ibuprofen cohort (ibuprofen mean dose of 2045 ± 246 mg/day) was associated with the worst outcomes for many of the CV endpoints and with a significantly higher risk of gastrointestinal and renal events [5].

SCOT (Standard care vs. Celecoxib Outcome Trial) was a pragmatic randomized trial of prescribed NSAIDs and CV safety that investigated the impact of switching half of the subjects prescribed NSAIDs in usual care to celecoxib. In this study, 7297 patients with osteoarthritis or rheumatoid arthritis, free from previous CV events, were randomized and followed up for an average of 3.2 years. In SCOT, the prescribed ibuprofen dose was lower than in PRECISION

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✉ Filippo Pigazzani
f.pigazzani@dundee.ac.uk

[1] Ninewells Hospital and Medical School, University of Dundee, Dundee, UK

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(675.9 ± 345.9 vs. 2045 ± 246 mg/day), and there was a very low CV event rate both in the selective and non-selective NSAIDs arms, suggesting that NSAIDs and celecoxib had acceptable CV safety in subjects free from established CV disease [6].

A recent Bayesian meta-analysis by Bally et al. [7] on the risk of acute myocardial infarction (AMI) with NSAIDs in real-world (observational) use showed an increased risk of AMI associated with all NSAIDs, selective and non-selective, with the greatest risk observed with higher doses and during the first month of treatment. In particular, this meta-analysis showed that use of ibuprofen for 8–30 days at doses > 1200 mg was particularly harmful (adjusted odds ratio 1.75). These findings suggest that NSAID users have a risk of cardiac events that depends primarily on drug dose and patient CV risk profile, a finding supported by the Doung et al. [2] study.

The Doung et al. [2] study appropriately matched the ibuprofen cohort with a paracetamol cohort to avoid protopathic and indication bias. However, paracetamol was chosen on the assumption of its low CV risk profile—an assumption that has been questioned. Recently, Sudano et al. [8] demonstrated that paracetamol is associated with a significant increase in ambulatory blood pressure in patients with coronary artery disease. A systematic review suggests that paracetamol should be used with caution in patients with established coronary artery disease [9]. In fact, because of the widespread use of paracetamol (twice that of ibuprofen), this drug accounted for twice the number of CV events (203 vs. 98), so maybe one should conclude that "All drugs are dangerous; and some may also be useful" [10].

Indication and protopathic biases and complex channeling effects exist in observational studies and only randomized trials can provide unbiased causal exposure and outcome measures. However, conventional randomized controlled trials are very expensive, time-consuming, and involve relatively small numbers of patients, and the potential to generalize their results is limited. Thus, large pharmacoepidemiology studies, such as the study by Doung et al. [2], are important.

The pattern of use of NSAIDs has changed in recent years due to the emerging evidence regarding associated CV risk, making it even more difficult to collect good real-world data on the risks of NSAIDs in the elderly and patients at higher CV risk in the future. The Duong et al. [2] study is a welcome addition to the literature.

Data from clinical trials, meta-analyses, and large pharmacoepidemiology studies have shown that low, analgesic doses of ibuprofen have a low risk for acute coronary disease when used in low CV risk people. However, in high CV risk subjects the PRECISION trial suggests that celecoxib could be safer, at least from a kidney and gastrointestinal point of view. Indeed, PRECISION had 'signals' that even naproxen was worse than celecoxib for mortality, renal events, and gastrointestinal events.

The study by Doung et al. [2] is an example of how efforts to advance the use of real-world data to generate real-world evidence continue to move forward and shows that they are able to provide useful and relevant information about the safety of commonly used medicines.

Compliance with Ethical Standards

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Conflict of Interest Thomas M. Macdonald was a principal investigator of the SCOT trial. Filippo Pigazzani, Isla Mackenzie, and Thomas M. MacDonald have no other conflicts of interest that are directly relevant to the content of this commentary.

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